Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Case Raport | Praca kazuistyczna
Pediatr Endocrino Diabetes Metab 2017;23,4:215-220
DOI: 10.18544/PEDM-23.04.0096


redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

# Is growth without IGF1 possible? A case report

## Czy wzrost bez udziału IGF1 jest możliwy? Opis przypadku

Maciej Flader, Dominika Zalas, Marek Niedziela

Department of Pediatric Endocrinology and Rheumatology, 2nd Chair of Pediatrics, Poznan University of Medical Sciences

**Abstract**
According to the growth hormone – insulin-like growth factor 1 axis (GH/IGF1 axis) theory, the actions of GH on promoting growth are mediated by IGF1. In the blood, IGF1, insulin-like growth factor 1 binding protein 3 (IGFBP3) and acid-labile subunit (ALS) form ternary complexes, hence the accumulation of IGF1. We report a case of 10-year-old male with short stature due to GH deficiency diagnosed with hypopituitarism. Therapy with recombinant human GH (rhGH) was initiated at 11 years and 4 months. After twenty three months on treatment clinical effects were as follows: increase in the patient's height by 19.2 cm (initial height 12.4 cm vs. 140.6 cm; hSDS -4.35 vs. -2.7; predicted adult height 176 cm vs. 182 cm, respectively). Despite good clinical response to the therapy, serum levels of IGF1 and IGFBP3 remained diminished: IGF1 – 28 ng/ml initially, vs. 23 ng/ml 19 months on therapy and IGFBP3 – 1116 ng/ml initially, vs. 1888 ng/ml after 11 months on therapy. We attempt to justify this phenomenon by reconsidering the IGF1-independent GH actions, assessing the endocrine role of hepatic IGF1 in comparison to the autocrine/paracrine role of its bone tissue fraction, and evaluating the functions of ALS. The exact explanation for the positive response to rhGH treatment without the expected increase in IGF1 in our patient remains unknown. Serum levels of IGF1 and IGFBP3 seem not always to be reliable markers of the response to rhGH treatment in GH-deficient patients.
**Key words**
short stature, pituitary hypoplasia, growth hormone deficiency, insulin-like growth factor 1 deficiency

**Streszczenie**
Zgodnie z teorią osi hormon wzrostu (GH) – insulinopodobny czynnik wzrostu 1 (IGF1) w działaniu GH na promowanie wzrostu komórek pośredniczy IGF1. W surowicy krwi IGF1 trzecie białko wiążące insulinopodobny czynnik wzrostu 1 (IGFBP3) oraz kwasolabilna podjednostka (ALS) tworzą potrójne kompleksy, które umożliwiają akumulację IGF1. Przedstawiamy przypadek 10-letniego chłopca z niskorosłością zależną od niedoboru GH, u którego zdiagnozowano niedoczynność przysadki. U pacjenta rozpoczęto terapię rekombinowanym ludzkim hormonem wzrostu (rhGH) w wieku 11 lat i 4 miesięcy. Odpowiedź po dwudziestu trzech miesiącach leczenia była następująca: zwiększenie wzrostu o 19.2 cm (wzrost początkowy: 121,4 cm, vs. 140,6 cm; hSDS początkowo -4,35 vs. -2,7, przewidywany wzrost ostateczny 176 cm vs. 182 cm). Pomimo dobrej odpowiedzi klinicznej stężenia IGF1 i IGFBP3 w surowicy pozostawały obniżone: IGF1 – 28 ng/ml początkowo vs. 23 ng/ml po 19 miesiącach leczenia, IGFBP3 – 1116 ng/ml początkowo vs. 1888 ng/ml po 11 miesiącach leczenia. Podejmując próbę wyjaśnienia tego zjawiska uwzględnić należy działanie GH niezależne od IGF1, endokrynną rolę frakcji IGF1 pochodzenia wątrobowego w porównaniu z frakcją IGF1 pochodzenia kostnego, działającą auto- i parakrynnie, ocenę funkcji ALS. Dokładne wyjaśnienie pozytywnej odpowiedzi na leczenie rhGH bez spodziewanego wzrostu IGF1 u naszego pacjenta pozostaje nieznane. Stężenia IGF1 oraz IGFBP3 w surowicy krwi nie zawsze są wiarygodnymi markerami działania rhGH stosowanego w somatotropinowej niedoczynności przysadki.
**Słowa kluczowe**
niskorosłość, hipoplazja przysadki, niedobór hormonu wzrostu, niedobór insulinopodobnego czynnika wzrostu 1



**prof. Marek Niedziela MD, PhD**
2nd Chair of Pediatrics, Poznan University of Medical Sciences
Szpitalna 27/33, 60-572 Poznan, Poland
tel. 61 849 14 81; tel/fax: 61 848 02 91
e mail: mniedzie@ump.edu.pl

Received: 14.11.2017
Accepted: 5.01.2018
Conflict of interests: none declared.

Pediatr Endocrinol Diabetes Metab 2017;23,4:215-220

## Introduction

Growth hormone is a peptide of 191 amino-acids, produced by the somatotrophs of the anterior pituitary. In the blood, GH molecules circulate, bound to the GH-binding proteins (GHBPs), which have the same amino-terminal amino-acid sequence as the amino-terminal sequence of the GH receptors (GHRs). Although the exact function of GHBP is not fully understood, it might modulate the activity of GH by reducing its availability to GHR or by prolonging its half-life. The GHR is composed of an intracellular, a transmembrane and an extracellular domain. The transduction of signal is based on the dimerization and internalization of the receptor, the activation of Janus tyrosine kinase 2 (JAK2), followed by its autophosphorylation as well as phosphorylation of the receptor, which leads to the activation of signal transducers, the most important of which are the transcription factors - STATs [2]. Among its many localizations, the GHRs occur in the liver, where they induce the synthesis and secretion of IGF1. Even though IGF1 is predominantly synthesized in the liver, it is also produced in multiple non-hepatic tissues, where it manifests an autocrine and paracrine effect [2].

IGF1 circulates in the blood in the ternary complex of 150kDa, together with IGF1 binding proteins, IGFBP3 or IGFBP5, and ALS. IGFBP3 is produced predominantly in the liver, and other sources of its production are also skin, bone, skeletal muscles, reproductive organs, and endothelium. IGFBP3 also has an IGF-independent mechanism of function as it can stimulate apoptosis and inhibit cell proliferation. ALS is synthesized exclusively in the liver due to GH stimulation. The ternary complex extends the half-life of IGF1 from 10 minutes to 12 hours, allows the accumulation of IGF1 in plasma; the hypoglycemic and other metabolic effects of IGF1 are controlled as the 150kDa complexes cannot cross the endothelium, and thus are unable to activate the insulin receptor [3]. In the organism, IGF1 is required for normal accrual of trabecular and cortical bone and linear growth – it is involved, among others, in chondrocyte proliferation and/or differentiation, hypertrophy of chondrocytes and osteoblast differentiation. It presents mitogenic, anti-apoptotic effects and can even cause malignant transformation. It also increases insulin sensitivity, largely by suppressing the secretion of GH from the pituitary as it is a part of GH negative feedback. Increased concentration of GH in human body, also as a result of GH supplementation /or substitution, should be parallel to increased levels of IGF1 and IGFBP3.

## Case report

A boy, aged 10 years and 9 months, was admitted to the Department of Pediatric Endocrinology and Rheumatology due to his short stature. The boy was born to non-consanguineous parents at the 37$^{th}$ week of gestation with a birth weight of 2740 g and birth length of 49 cm, no abnormalities were observed. The family history was negative for heritable diseases concerning short stature. The patient's target height was not evaluated since the child was adopted and no detailed parental data were available. On admission to hospital, the patient weighed 30.0 kg (-1,4 SD) with a height of 119.3 cm (hSDS -4,1). On physical examination no further abnormalities were found; motor development was normal. The patient had just entered puberty – axilarche 1, pubarche 1, testes 4 ml. A year before the patient had been diagnosed with secondary hypothyroidism and had been administered L-thyroxine (L-T4) ever since. The initial dose of LT4 was 25mcg, later on it was increased to 50mcg. The levels of TSH and FT4 in further tests reached reference levels, as presented in Table I.

Tests of the pituitary reserve of growth hormone with the use of clonidine (0.15 mg/m2; p.o.) and glucagon (0.03 mg/kg; i.m.) as well as the sleep test were performed (Table II). Plasma GH concentrations were determined by immunoradiometric assay for hGH (hGH-IRMA KIP1081, DIAsource, ImmunoAssays SA, Nivelles, Belgium). The detection limit was 0.04 $\mu$IU/ml (conversion factor: 1 $\mu$IU hGH-IRMA Calibrator = 0.33 ng). The maximum GH peak release was severely diminished reaching only up to 2% of its normal range – 0.2 ng/ml (N >10 ng/ml). Radioimmunoassay (RIA) with the use of IGF1-RIA-CT KIP1588 kit (DIAsource, ImmunoAssays SA, Nivelles, Belgium) was performed for the quantitative measurement of plasma IGF1. The threshold sensitivity of the assay was 3.4 ng/ml. IGFBP3 concentration was measured by immunoradiometric assay with the use of IGFBP3-IRMA KIP1171 (DIAsource, ImmunoAssays SA, Nivelles, Belgium). The detection limit was 17.3 ng/ml. The level of IGF1 (28 ng/ml; N:181–656 ng/ml) and the level of IGFBP3 (1116.0 ng/ml; N: 2935–4524 ng/ml) were also very severely below the normal range. MRI of the head revealed pituitary hypoplasia, the patient was diagnosed with combined pituitary hormone deficiency (TSH and GH). Treatment with rhGH was introduced at the age of 11 years and 4 months. Tests prior to rhGH therapy revealed even lower levels of IGF1 (0 ng/ml) and IGFBP3 (795 ng/ml). The adjusted initial dose of rhGH was 0.8 mg per day (Omnitrope/Genotropin, 0.026 mg/kg, 0.18 mg/kg/week; both products were used in the study period as a result of national competition for providing rhGH every year). The bone age (6 years) was retarded by 4 years in comparison to the chronological age of the patient. With a very good clinical response to rhGH therapy, the levels of both GH responders, IGF1 and IGFBP3 remained severely diminished, with IGF1 reaching a peak level of only 72 ng/ml (Table III).

Glycated haemoglobin level was between 5.4%-5.8% during the whole period of treatment. Insulin levels (fasting) oscillated around 4.1 $\mu$U/mL.

## Discussion

Our patient suffers from combined pituitary hormone deficiency due to pituitary hypoplasia, which resulted in severe GHD and postnatal growth deficit, with a height of -4.35 SDS at the age of 10 years. Before the initiation of the therapy, a

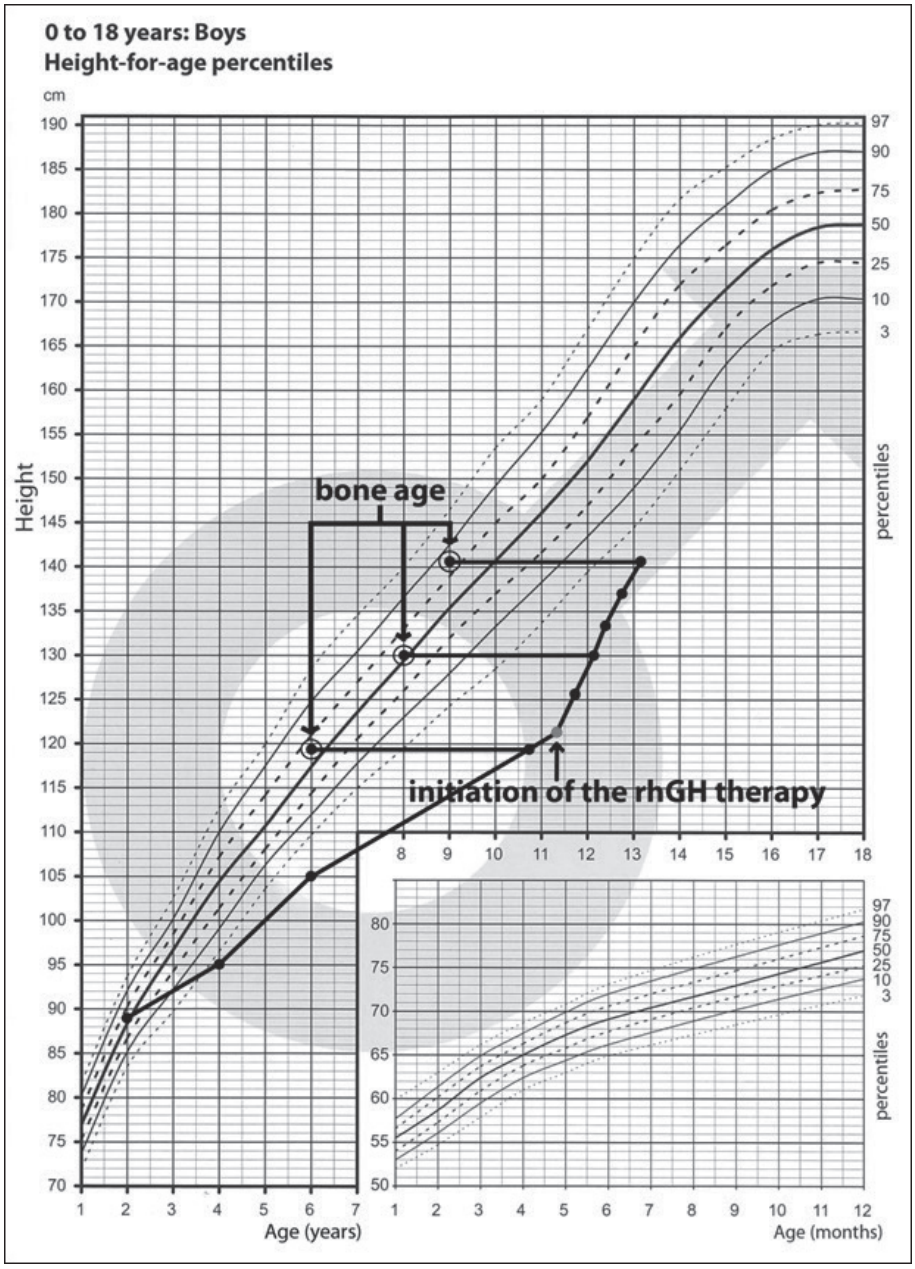


**Fig. 1.** Patient's growth curve before and after the initiation of rhGH treatment. The growth rate before rhGH therapy was 3.6 cm/y. In the first year of rhGH therapy the patient'sheight velocity was 11.4 cm, and improved by 7.8 cm within the next 11 months. The patientis on the way to reaching the 3rd percentile. The auxological parameters, those at the initiation of rhGH treatment and after 23 months of therapy, were as follows: height – 121,4 cm vs. 140,6 cm; hSDS–4,35 vs. -2,7. During 23 months of therapy bone age advanced by 3 years. Predicted adult height improved – 182 cm vs.initial 176 cm (based on Bayley-Pineau formula). 181x251mm (300 x 300 DPI)

***Ryc. 1.*** *Krzywa wzrastania pacjenta przed i po włączeniu leczenia ludzkim rekombinowanym hormonem wzrostu (rhGH). Tempo wzrastania przed leczeniem rhGH wynosiło 3,6 cm/rok. W pierwszym roku terapii rhGH tempo wzrastania wynosiło 11,4 cm, a następnie 7,8 cm w ciągu kolejnych 11 miesięcy. Parametry auksologiczne pacjenta w chwili rozpoczęcia terapii rhGH oraz po 23 miesiącach leczenia prezentują się następująco: 121,4 cm vs 140,6 cm; hSDS -4,35 vs -2,7. W ciągu 23 miesięcy leczenia wiek kostny pacjenta awansował o 3 lata. Prognozowany wzrost ostateczny uległ poprawie – 182 cm vs wyjściowo 176 cm (określony metodą Bayley-Pineau). 182x253mm (300 x 300 DPI)*

Pediatr Endocrinol Diabetes Metab 2017;23,4:215-220

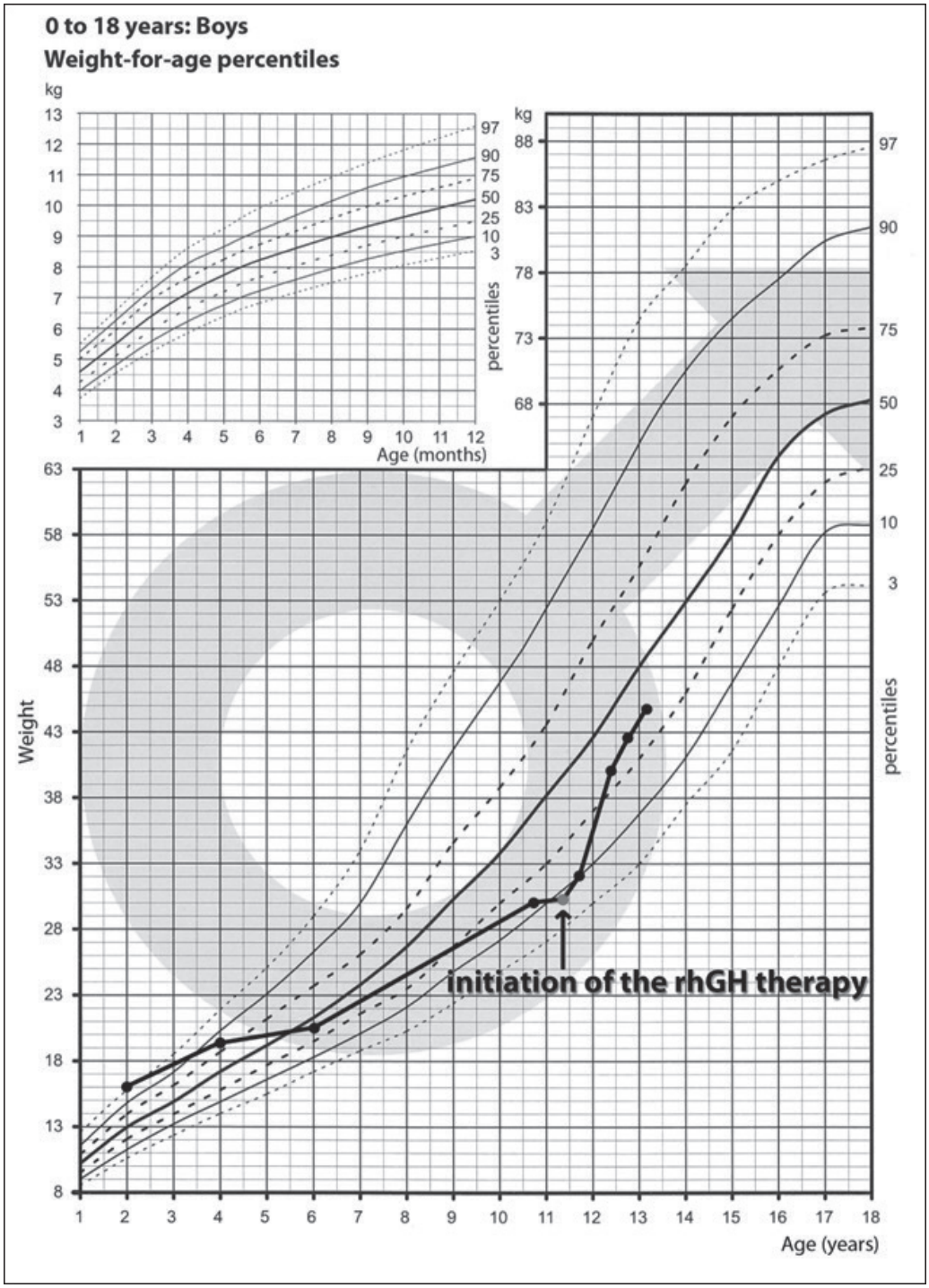


**Fig. 2.** Development of the patient'sweight curve. Percentile position, rose from below the 10th percentile to the range between the 25th and 50th. The patient's BMI at first admission was 20.48 and after 23 months of therapy increased to 22.61 [kg/m$^2$]. 182x253mm (300 x 300 DPI)

***Ryc. 2.*** *Krzywa przedstawiająca masę ciała pacjenta na siatce centylowej. W okresie leczenia pacjent z 10 centyla awansował do przedziału pomiędzy 25 a 50 centylem. Wskaźnik BMI pacjenta wzrósł z wyjściowej wartości 20.48 do 22.61 [kg/m2] po 23 miesiącach terapii. 182x253mm (300 x 300 DPI)*

**Table I.** TSH and thyroid hormone levels (abnormal values are given in bold)
***Tabela I.*** *Stężenie TSH i wolnych hormonów tarczycy (wartości poza normą wytłuszczono)*

| Time / Czas / TSH and FT4 | at 1st admission / Pierwsze przyjęcie do szpitala | Initiation of therapy / Rozpoczęcie leczenia rhGH | 8th month of therapy / 8. miesiąc terapii | 11th month of therapy / 11. miesiąc terapii | 19th month of therapy / 19. miesiąc terapii | 23rd month of therapy / 23. miesiąc terapii |
|---|---|---|---|---|---|---|
| TSH N: 0,47-4,64 ulU/mL | 2.82 | 1.95 | 3.11 | 4.27 | 5.59 | 3.14 |
| FT4 N:0,71-1,85 ng/dl | **0.68 ↓** | 1.04 | 0.80 | **0.68 ↓** | 0.97 | 0.96 |

**Table II.** GH serum levels (ng/ml) in spontaneous (during sleep) and pharmacological tests
***Tabela II.*** *Stężenie hormonu wzrostu (ng/ml) zmierzone podczas snu oraz w testach farmakologicznych*

| Time Czas (min) | GH after onset of sleep Test po zaśnięciu | GH after Clonidine Test po klonidynie | GH after Glucagon Test po glukagonie | |
|---|---|---|---|---|
| **0`** | 0,1 | 0,2 | **0`** | 0,2 |
| **30`** | 0,2 | 0,2 | **60`** | 0,2 |
| **60`** | 0,1 | 0,2 | **90`** | 0,2 |
| **90`** | 0,2 | 0,2 | **120`** | 0,2 |
| **120`** | 0,2 | 0,2 | **150`** | 0,2 |

**Table III.** IGF1 and IGFBP3 serum levels before and duringrh GH treatment
***Tabela III.*** *Stężenie IGF1 oraz IGFBP3 przed i w czasie terapii rhGH*

| Time / Czas / IGF1 and IGFBP3 | 1st admission / Pierwsze przyjęcie do szpitala | Initiation of therapy / Rozpoczęcie leczenia rhGH | 4th month of therapy / 4. miesiąc terapii | 8th month of therapy / 8. miesiąc terapii | 11th month of therapy / 11. miesiąc terapii | 19th month of therapy / 19. miesiąc terapii |
|---|---|---|---|---|---|---|
| **IGF1 [ng/ml]** | 28 | 0 | 34 | 38 | 72 | 23 |
| **IGFBP3 [ng/ml]** | 1116 | 795 | 1076 | NA | 1888 | NA |

decline in the growth velocity and systematic decrease of the percentile position below the 3rd percentile on the height-for-age growth chart was observed. The patient was administered rhGH in a dose of 0.026 mg/kg/day and presented very good catch-up growth. Over a 23-month period the patient's height increased by 19.2 cm, and at the age of 13 years and 3 months the patient's height was 140.6 cm (-2.7 SDS) with the improvement of his predicted adult height (PAH) from 176 to 182 cm. However, despite this very good response to rhGH therapy, we did not observe the expected rise in the levels of both, IGF1 and IGFBP3 (Table III), which remained severely diminished. Therefore, two issues need to be explained in the presented case – why the plasma IGF1 concentration did not increase significantly in a pubertal boy and therefore, how the positive response to rhGH therapy was achieved?

Keeping in mind the effects of insulin on growth, such as the increase in collagen synthesis, alkaline phosphatase production and osteoblast differentiation; due to the normal level of insulin and normal levels of glycated haemoglobin, we propose that in this case the positive response to rhGH therapy is associated precisely with rhGH and have excluded the effects of insulin on growth.

The thyroid hormones are also involved in the postnatal development of the skeleton. Clinical observations confirm that an excess or shortage of thyroid hormones causes abnormalities in linear growth and bone maturation. Thyroid hormones cause an increase in IGFR mRNA and enable the differentiation of chondrocytes, while T3 anabolic actions during the period of growth stimulate peak bone mass accrual. However, in the presented case no acceleration in growth velocity was observed during the first year of L-thyroxine therapy (prior to rhGH treatment), which suggests that, in the presented case, the direct effects of GH/IGF1 cascade are responsible for catch-up growth.

According to the original 'somatomedin hypothesis' introduced by Daughaday in 1957 et al.[11], the 'sulfation factor', later on renamed to somatomedin, now referred to as insulin-like growth factor1 acts as a mediator of the growth hormone function. The synthesis of IGF1, predominantly in the liver, is GH-induced. It acts in an endocrine manner. In the 'dual effector theory' (1985) Green et al. claimed that GH acts both directly and indirectly on target cells. The indirect role of GH is also IGF1-mediated, but the IGF1-induced clonal expansion of chondrocytes results from its autocrine and paracrine mechanism of function, as it is synthesized in multiple tissues of the body, including the cartilage [12]. Present data support the complex role of GH/IGF1 axis, and involve the assumptions of both Daughaday and Green, the liver-derived IGF1 acts in endocrine manner, whereas the IGF1 which is produced in other tissues acts in an autocrine and paracrine manner. Apart from this indirect role, GH also acts IGF1-independently on osteoblasts to stimulate bone formation and also directly promotes chondrocyte proliferation and likely generation [14].

Studies have been conducted to evaluate the direct and indirect role of GH. In the experiment of Wang et al. ghr null mice were produced; the tibial linear growth rate in these animals between postnatal days 20 and 40 (a time of peak GH effect during normal longitudinal growth) was reduced by about 65%, in comparison to igf1 null mice which suffered 35% tibial linear growth rate reduction. This confirmed the hypothesis that growth would be more affected by the absence of GH rather than IGF1. The IGF1 independent mechanisms of growth hormone function have a crucial role in promoting chondrocyte proliferation and likely generation. However, bearing in mind Laron's syndrome, in which growth retardation is observed together with low IGF1 despite high GH levels, the GH independent role would probably be insufficient to achieve the good response to rhGH therapy in the discussed case. Several experiments have been conducted to assess the impact of the hepatic fraction of IGF1 and IGF1 produced in other tissues on growth processes.

The experiments of Yakar and Sjogren confirm that the liver is the pivotal organ in IGF1 synthesis, but provide direct evidence that it is its autocrine or paracrine mechanism of function that plays the major role in IGF1-induced processes of growth. In both of these studies the Cre/loxP recombination system was used in order to delete the igf1 gene exclusively in the liver. The concentration of circulating IGF1 in the mice produced was reduced by 75% in both studies. Nevertheless, the growth, determined by body length, body weight and femoral length, was indistinguishable between the liver-derived igf1 null mice and their wild-type littermates [16,17]. These studies resemble, to some extent, the case of our patient and may suggest that apart from hypopituitarism, the patient lacks the hepatic pool of IGF1. The study of Yong et al. is coherent with the studies of Yakar and Sjogren. Yong used the Cre/lox-mediated model of tissue-specific deletion of growth hormone receptor gene, in order to distinguish the effects of GH from the effects of hepatic IGF1. Almost total GHR absence in the liver resulted in an over 90% decrease in the IGF1 plasma level and a significant reduction in total bone density, yet no effects on body or bone linear growth were observed. Yong et al. suggest that circulating IGF1 amplifies the effects of GH on growth and at the same time reduces the catabolic effects of GH. In these mice, the circulating level of GH was increased 4-fold and they suffered from the diabetogenic effects of growth hormone, including insulin resistance, glucose intolerance, increased circulating free fatty acids, liver steatosis [18]. According to this study, it is the GH receptors in the liver that may be functioning improperly in our patient. A combination of hypopituitarism with severe GHD, and hepatic GHR malfunctioning would explain why the patient did not present the abundant metabolic effects of growth hormone.

The study on the acid-labile subunit of the ternary complex of IGF1, IGFBP3 and ALS is also consistent with the studies which compared the endocrine vs. autocrine/paracrine mechanism of IGF1 function [3]. In the blood, ALS circulates in an excessive amount over the levels of the other elements of the ternary complex. In order to examine the role of ALS itself, Boisclair et al. produced als KO-mice. In these mice the ternary complexes were absent; these mice suffered a reduction in plasma concentrations of IGF1 and IGFBP3 compared to their

wild-type siblings (62 and 88% reductions, respectively). These reductions were observed despite the lack of any decline in the IGF1 and IGFBP3 synthesis in the liver, and this study confirmed that ALS is crucial for the accumulation of both of these proteins. However, in the produced mice the growth deficit by adulthood reached only 13% [3].

Few IGF1/ALS deficient patients have been described. David et al. describe two ALS-deficient patients [19]. The height of patient 1, a 13.3-year-old boy from a consanguineous family, was -3.2SDS, bone age was 12.5 years and he was Tanner stage II, no pubertal delay was observed in this case. The height of patient 2 was -2.8SDS for his age and sex, at the age of 10.6 years, his bone age was 6.5 years, he was considered prepubertal. In the biochemical evaluation, the levels of IGF1, IGFBP3 and ALS in patients 1 and 2 were severely diminished, which occurred despite normal GHBP levels, exaggerated in case of patient 1 and asignificantly increased concentration of GH in patient 2, after provocation tests [19]. Domene et al. presented a case report of a 17-year-old male patient with complete ALS absence. At the age of 14.6 years the patient's height was -2.05SDS, the patient was Tanner stage 1. The patient presented normal responses to GH stimulation tests, the level of IGF1 was -5.3SDS and IGFBP3 was -9.7SDS for the chronologic age. Domene took into consideration autocrine and paracrine mechanisms of IGF1 action as a possible explanation for only mild retardation of growth, but was unable to measure the levels of free IGF1 [20]. Another study of Domene et al. described a patient with IGF/ALS deficit, whose height was -2.00SDS at the age of 15.3 years, he was Tanner stage 1 [21]. The patient was diagnosed with non-GH deficient short stature, however therapy with rhGH was started. Growth velocity improved from 6.2 cm/y before rhGH therapy to 8.0 cm/y after rhGH therapy, at the age of 16.1 years, his height was -1.0SDS. Domene et al. considered the clinical and biochemical response to rhGH therapy as 'modest', the levels of IGF1 and IGFBP3 remained severely reduced [21]. The case of our patient resembles, to some extent, the cases presented by David and Domene. We may therefore suppose that the low circulating concentration of IGF1 in case of the discussed boy may be the result of impaired ALS synthesis in the liver.

The role of IGF2 on the process of growth has also been taken into consideration. Wang et al. hypothesized that it may mediate the action of GH on chondrocyte proliferation, as they observed increased levels of igf2 mRNA in igf1 null mice and decreased levels in ghr null mice. igf2 KO-mice were produced and the growth deficit in the femoral length in these mice was only 10–15% in comparison to their wild-type littermates. Studies confirmed that IGF2 plays a minimal role in bone mineral density accrual with BMD decreased by 18% in igf2 KO-mice compared with corresponding control mice.

The exact explanation for the positive response to GH treatment without the expected increase in IGF1 in the presented patient remains unknown. Serum levels of IGF1 and IGFBP3 seem not always to be reliable markers of response to rhGH treatment in GH-deficient patients. Further molecular investigations in this patient will be of great significance for better understanding of GH/IGF1 action in the human body.

Źródła finansowania pracy:

Badania statutowe (nr 502-01-1104118-06037) Kliniki Endokrynologii i Reumatologii Dziecięcej Uniwersytetu Medycznego im. Karola Marcinkowskiego w Poznaniu

## References

1. Leung DW, Spencer SA, Cachianes G et al. *Growth hormone receptor and serum binding protein: purification, cloning and expression.* Nature. 1987;330:537-543.
2. Boisclair YR, Rhoads RP, Ueki I et al. *The acid-labile subunit (ALS) of the 150 kDa IGF-binding protein complex: animportant but forgotten component of the circulating IGF system.* J Endocrinol. 2001;170(1):63-70.
3. Hong J, Zhang G, Dong F, Rechler MM. *Insulin-like Growth Factor (IGF)-binding Protein-3 Mutants That Do Not Bind IGF-I or IGF-II Stimulate Apoptosis in Human Prostate Cancer Cells.* J Biol Chem. 2002;277(12):10489-10497.
4. Hwa V, Oh Y, Rosenfeld RG. *The insulin-like Growth Factor-binding protein (IGFBP) superfamily.* Endocr Rev. 1999;20(6):761-787.
5. Valentinis B, Baserga R. *IGF-I receptor signalling in transformation and differentiation.* Mol Pathol. 2001;54(3):133-137.
6. Ohlsson C, Mohan S, Sjögren K et al. *The Role of Liver-Derived Insulin-Like Growth Factor*. I. Endocr Rev. 2009;30(5):494-535.
7. Bayley N, Pinneau SR. *Tables for predicting adult height from skeletal age: revised for use with Greulich Pyle hand standards.* J Pediatr. 1952;50:432-441.
8. Fulzele K, Riddle RC, DiGirolamo DJ et al. *Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition.* Cell. 2010;142(2):309-319.
9. Wang L, Shao YY, Ballock RT. *Thyroid hormone-mediated growth and differentiation of growth platechondrocytes involves IGF-1 modulation of beta-catenin signaling.* J Bone Miner Res. 2010;25(5):1138-1146.
10. Williams GR. *Actions of thyroid hormones in bone.* Endokrynol Pol. 2009;60(5):380-388.
11. Daughaday WH. *Growth hormone axis overview – somatomedin hypothesis*. Pediatr Nephrol. 2000;14(7):537-540.
12. Green H, Morikawa M, Nixon T. *A dual effector theory of growth-hormone action.* Differentiation. 1985;29(3):195-198.
13. Chihara K, Sugimoto T. *The action of GH/IGF-I/IGFBP in osteoblasts and osteoclasts.* Horm Res. 1997;48(Suppl 5):45-49.
14. Wang J, Zhou J, Cheng CM et al. *Evidence supporting dual, IGF-I--independent and IGF-I-dependent, roles for GH in promoting longitudinal bone growth.* J Endocrinol. 2004;180(2):247-255.
15. Laron Z. *An update on Laron syndrome.* Arch Dis Child. 1993;68(3):345-346.

 

16. Sjögren K, Liu JL, Blad K et al. *Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice.* Proc. Natl. Acad. Sci. USA. 1999;96(12):7088-7092.
17. Yakar S, Liu JL, Stannard B et al. *Normal growth and development in the absence of hepatic insulin-like growth factor* I. Proc. Natl. Acad. Sci. USA 1999;96:7324-7329.
18. Fan Y, Menon RK, Cohen P et al. *Liver-specific deletion of the growth hormone receptor reveals essential role of growth hormone signaling in hepatic lipid metabolism.* J Biol Chem. 2009;284(30):19937-19944.
19. David A, Rose SJ, Miraki-Moud F et al. *Acid-labile subunit deficiency and growth failure: description of two novel cases.* Horm Res Paediatr. 2010;73(5):328-334.
20. Domené HM, Bengolea SV, Martínez AS et al. *Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene.* N Engl J Med. 2004;5:570-577.
21. Domené HM, Scaglia PA, Lteif A et al. *Phenotypice ffects of null and haploin sufficiency of acid-labile subunit in a family with two novel IGFALS gene mutations.* J Clin Endocrinol Metab. 2007;92(11):4444-4450.
22. Mohan S, Richman C, Guo R et al. *Insulin-like growth factor regulates peak bone mineral density in mice by both growth hormone-dependent and -independent mechanisms.* Endocrinology. 2003;144(3):929-936.